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PRE-APPEAL BRIEF REQUEST FOR REVIEW		Docket Number: 07917-0183001
I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to Mail Stop AF, Commissioner for Patents, Box 1450, Alexandria, VA 22313-1450. Date of Deposit Signature Typed or Printed Name of Person Signing Certificate	Application Number 10/767,019	Filed January 29, 2004
	First Named Inventor George E. Wright	
	Art Unit 1623	Examiner Roy P. Issac

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a Notice of Appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

☒ attorney or agent of record
(Reg. No.) 50,429

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34

Signature

Janice Kugler DeYoung
Typed or printed name

(617) 542-5070
Telephone number

September 12, 2008
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ Total of **no.** forms are submitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: George E. Wright	Art Unit	: 1623
Serial No.	: 10/767,019	Examiner	: Roy P. Issac
Filed	: January 29, 2004	Conf. No.	: 4717
Title	: NOVEL ANTIHERPES DRUG COMBINATIONS		

MAIL STOP AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REMARKS SUBMITTED WITH PRE-APPEAL BRIEF REQUEST FOR REVIEW

Pursuant to United States Patent and Trademark Office OG Notices: 12 July 2005 New Pre-Appeal Brief Conference Pilot Program, a request for a review of identified matters on appeal is hereby submitted with a Notice of Appeal. Review of identified matters by a panel of Examiners is requested because the rejections of record are clearly not proper in view of a clear legal or factual deficiency in the rejections.

Claims 1-19 and 32-46 are pending; claims 41 and 42 are withdrawn, leaving claims 1-19, 32-40, and 43-46 presently under consideration.

Claims 1-19 and 32-40 stand rejected under 35 U.S.C. § 112, second paragraph for allegedly being indefinite in using the term "analog" in the claims. Second, claims 1-19 and 32-40, 43-46 stand rejected under 35 U.S.C. § 112, first paragraph for allegedly lacking enablement. Finally, claims 1-19 and 32-40, 43-46 have been rejected as being allegedly obvious over Wright, U.S. Patent No. 5,646,155 ("Wright '155") in view of Naesens et al., Herpes, 8(1), 2001 ("Naesens"). Applicants will address each of these grounds of rejection in turn.

Amended claim 1 features compositions that include a combination of an inhibitor of Herpes simplex virus thymidine kinase that is selected from the group consisting of 2-phenylamino-9-substituted-6-oxopurines and 2-phenylamino-9H-6-oxopurines, or an ester, salt, or solvate thereof, and an antiherpes substance that inhibits viral DNA replication that includes one or more of (1) a pre-phosphorylated or phosphonate nucleoside analog; (2) a pyrophosphate analog; and (3) a nucleoside analog, or any combination thereof, or an ester, salt, or solvate thereof.

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Amended claim 32 features kits for treatment of a Herpes simplex virus infection in a mammal that include (a) an inhibitor of Herpes simplex virus thymidine kinase that is selected from the group consisting of 2-phenylamino-9-substituted-6-oxopurines and 2-phenylamino-9H-6-oxopurines, or an ester, salt, or solvate thereof, (b) an antiherpes substance that inhibits viral DNA replication that includes one or more of (1) a pre-phosphorylated or phosphonate nucleoside analog; (2) a pyrophosphate analog; and (3) a nucleoside analog, or any combination thereof, or an ester, salt or solvate thereof, and instructions for administering (a) and (b) concurrently or within a sufficiently close time to achieve coexistent concentrations of (a) and (b) in subject.

Independent claims 43 and 45, which are directed to a composition and a kit, require specific inhibitors and antiherpes substances; namely 2-phenylamino-9-(4-hydroxybutyl)-6-oxopurine, or an ester, salt, or solvate thereof as inhibitor, and one or more of foscarnet, acyclovir, and cidofovir or an ester, salt, or solvate of any of these antiherpes substances.

As described in the present specification, the inhibitor of Herpes simplex virus (HSV) thymidine kinase (TK), and the antiherpes substance that inhibits viral DNA replication provide an unexpected synergistic effect in activity against recurrent Herpes simplex infections, and Herpes simplex encephalitis. Except for active antiviral therapy, which inhibits viral DNA replication (e.g., by inhibiting viral DNA polymerase), and prophylactic acyclovir in certain cases, there are few (if any) therapies available to prevent recurrences, or to prevent asymptomatic viral shedding and infectivity. This invention, therefore, represents a major breakthrough in the treatment of recurrent Herpes simplex infections, and Herpes simplex encephalitis.

Rejection under 35 U.S.C. § 112, Second Paragraph

Regarding the rejection of claims 1-19 and 32-40 for using the term "analog," the Applicant respectfully submits that the metes and bounds of the term "analogs" with respect to the claimed classes of molecules is well understood by those of ordinary skill working in the field of herpes infections. As evidence that this is indeed the case, Applicant previously submitted[1] excerpts from a NIAID Chemical Database (of the National Institutes of Health) that

[1] With the AMENDMENT IN REPLY TO OFFICE ACTION DATED JUNE 13, 2007, submitted December 13, 2007

describes "nucleoside analogs," such as AZT, 3TC, ddI, ddC, D4T and abacavir succinate; a GlaxoSmithKline datasheet for ZOVIRAX® (acyclovir), describing acyclovir as "a synthetic nucleoside analogue," and a paper describing the rational design of antiviral drugs, such as "nucleoside analogs" and "pyrophosphate analogs." Since a person of ordinary skill in the art would understand the term "analogs" in this context, the term is definite.

Rejection under 35 U.S.C. § 112, first paragraph

Regarding the rejection of claims 1-19, 32-40, and 43-46, the Applicant respectfully submits that the full scope of the claims is enabled. First, Applicant is claiming compositions and kits and not methods of use. Thus, the specification must teach how to make and how to administer the claimed compositions and how to use the kits. Applicant submits that the specification fully meets this requirement.

The claimed compositions require two components, an inhibitor of HSV TK and an antiherpes substance that inhibits viral DNA replication, and the specification fully describes how to obtain or make each of these components and how to combine them. For example, in paragraph [0030] of the published application, Applicant references Wright '155, and the compound HBPG. Wright '155 discloses numerous HSV TK inhibitors, along with their synthesis and characterization. For example, Table 1 of Wright '155 shows the concentration of nine compounds, the last being HBPG, at which fifty percent of either HSV1 or HSV2 TK inhibition is observed. Thus, having access to the present specification, along with Wright '155, a person of ordinary skill in the art would have in their possession the suitable TK inhibitors, and would have test methods for determining HSV TK inhibition for other suitable TK inhibitors that may not be described in Wright '155. Applicant respectfully submits that an inhibitor of Herpes simplex virus thymidine kinase, as each independent claim requires, is fully enabled.

With respect to an antiherpes substance that inhibits viral DNA replication, this class of compounds is readily known to a person of ordinary skill in the art (see, e.g., the NIAID Chemical Database referenced above). The present specification also discloses numerous examples. Applicant provided working examples with foscarnet, acyclovir, and cidoforvir, and notes this is a structurally diverse set of molecules. The test results in the application as filed support Applicant's assertion that since three such structurally diverse molecules worked, and other molecules within the classes represented by those molecules work by exactly the same

mechanism, that other molecules within those classes of molecules would also work in a similar fashion. Thus, Applicant respectfully submits that the antiherpes substance that inhibits viral DNA replication is fully enabled as well.

With respect to the claimed combination of the HSV TK inhibitor, and an antiherpes substance, the specification also describes how to combine these two components and how to administer them concurrently (see, e.g., paragraph [0041]).

Thus, Applicant respectfully submits that a person of ordinary skill armed with the teachings of Wright '155 and the present specification could fully make and use the claimed invention without undue experimentation because the level of skill in the art is high ("PhD, M.D. or equivalent advanced degree" as admitted by the Office Action mailed March 12, 2008, at page 5), and because considerable guidance and direction is given in the specification, as discussed above. Thus, Applicant respectfully submits that the claims are fully enabled, and requests that the rejection be withdrawn.

Rejection under 35 U.S.C. § 103

Claims 1-19 and 32-40, 43-46 have been rejected as being allegedly obvious over Wright '155 in view of Naesens et al., Herpes, 8(1), 2001 ("Naesens"). The Office Action mailed March 12, 2008 at page 11 cites a passage in Wright '155 found at col. 9, lines 59-62, which is reproduced below.

> The compounds of the invention can be used as the sole active agents, or can be used in combination with other active ingredients, e.g., direct antiviral drugs, growth factors which could facilitate neuronal survival in neurological diseases, or peptidase or protease inhibitors.

Applicant respectfully submits that the passage cited in Wright '155 (above) is vague, and would not have led a person of ordinary skill in the art to the presently claimed inventions. For the sake of argument, even if the Office has established a *prima facie* case of obviousness, a conclusion that is not shared by applicant, the present application provides clear evidence of unexpected results that rebuts any such a conclusion. For example, at paragraph [0049], the present application describes experiments with respect to a combination of HBPG and foscarnet:

> The results of Table 1 establish dose-response relationships for the effect of each compound when administered individually to mice

> to be used against encephalitis caused by HSV1 and HSV2. The results of Table 2 illustrate the effect of combining suboptimal doses of HBPG and foscarnet in treatment of HSV2 encephalitis, **showing clear synergistic effect of the combinations**. For example, the combination of 50 mg/kg of each compound protected 50% of mice from HSV2 encephalitis, whereas simple addition of the compound effects would be expected to protect only 10% of animals. The combination of 100 mg/kg of HBPG and 50 mg/kg of foscarnet protected 80% of mice from HSV2 encephalitis, whereas simple addition of the compound effects would be expected to protect 30% of animals. (*emphasis added*)

Synergy was also found with respect to combinations of HBPG and cidofovir (see Table 4), and HBPG and acyclovir (see Table 6). These synergistic and unexpected results are exactly the type of evidence the U.S. Supreme Court suggested are useful to rebut an obviousness rejection in KSR v. Teleflex, 127 S. Ct. 1727 (2007). Thus, Applicant respectfully submits that these unpredictable results render the claimed inventions patentable. Accordingly, *prima facie* obviousness has not been established and the rejection is improper.

Applicants respectfully submit that none of the rejections made by the Examiner are proper for at least the reasons set forth above. As such, Applicants respectfully submit that all claims, as presented in Applicants' AMENDMENT IN REPLY TO OFFICE ACTION DATED JUNE 13, 2007, submitted December 13, 2007, are in condition for allowance.

Respectfully submitted,

Date: Sept. 12, 2008

Janice Kugler DeYoung
Reg. No. 50,429

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906